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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/560,372	04/28/2000	Alan R. Tall	61766/JPW/GJG	3550

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EXAMINER
PARAS JR, PETER

ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 01/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/560,372	TALL, ALAN R.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18-25 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-16,18-25 and 49* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 November 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's amendment received on 7/8/02 has been entered. Claims 1, 8, 15, 20, and 49 have been amended. Claims 17 and 26-48 have been cancelled. Claims 1-16, 18-25 and 49 are pending and are under current consideration.

Claim Objections

The previous objection to claim 11 has been withdrawn in light of Applicant's amendment to the claim.

Drawings

The corrected or substitute drawings were received on 4 November 2002. These drawings are accepted by the Examiner.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-15, 18-25 and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The previous rejection is maintained for the reasons of record advanced on pages 2-5 of the Office action mailed on 1/3/02.

Applicant's arguments filed 7/8/02 have been fully considered but they are not persuasive. Applicants have argued that the claimed invention is directed to homologs of SEQ ID NO: 1. Applicants further argue that the instant specification provides guidance that would allow the skilled artisan to produce DNA sequences that are 95% homologous with SEQ ID NO: 1. Applicants assert that the claimed promoter's activity comes from molecular interaction and that all such activity would not be eliminated merely by small changes in the nucleotide sequences of the promoter.

In response, the Examiner maintains that the evidence of record has not described any variant sequences of the nucleotide sequence set forth in SEQ ID NO: 1 embraced by the claims (for clarity, variants include those nucleotide sequences that share [87% or 95%] homology with the nucleotide sequence set forth in SEQ ID NO: 1 and those sequences that hybridize to the nucleotide sequence set forth in SEQ ID NO: 1). Possession may be shown by reduction to practice or by describing the relevant identifying characteristics of the claimed nucleotide sequences. The specification discloses isolation of a nucleotide sequence (SEQ ID NO: 1) that is a novel human ABC promoter and does not disclose other mammalian ABC promoters or human ABC promoters or other ABC promoters from other cell types. There is no evidence on the record of a relationship between the structure of any ABC promoter and the claimed human ABC promoter that would provide any reliable information about the structure of other ABC promoters within the genus. There is no evidence on the record that the claimed human ABC promoter as set forth in SEQ ID NO: 1 had a known

structural relationship to any other ABC promoter sequences or the variant nucleotide sequences embraced by the claims; the specification discloses only a single human ABC promoter. There is no evidence of record that would indicate that any of the claimed variants of SEQ ID NO: 1, even have the biological activity of the claimed human ABC promoter set forth in SEQ ID NO: 1. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus, because a human ABC promoter sequence is not representative of the claimed genus. Consequently, since Applicant was in possession of only the human ABC promoter as set forth in SEQ ID NO: 1 and since the art recognized variation among the species of the genus of nucleotide sequences of ABC promoters, the human ABC promoter was not representative of the claimed genus. Therefore, Applicant was not in possession of the genus of ABC promoters as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Accordingly, the rejection is maintained for the reasons of record.

Claims 10-16, 18-25 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleotide

sequence set forth in SEQ ID NO: 1, a host cell transformed *in vitro* with a recombinant expression construct comprising the nucleotide sequence set forth in SEQ ID NO: 1 operably linked to a foreign nucleotide sequence encoding a polypeptide of interest and an *in vitro* method of expressing foreign DNA in a host cell using the same recombinant expression construct, does not reasonably provide enablement for variants of the nucleotide sequence set forth in SEQ ID NO: 1, host cells transformed *in vivo*, and methods of transforming host cells *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The previous rejection is maintained for the reasons of record advanced on pages 5-8 of the Office action mailed on 1/3/02.

Applicant's arguments filed 7/8/02 have been fully considered but they are not persuasive. Applicants have argued that methods for preparing recombinant expression constructs and expressing them *ex vivo* and *in vivo* were well known to the skilled artisan at the time of filing of the subject application. See pages 10-11 of the amendment.

In response, the Examiner maintains that host cells transformed *in vivo* and methods of transforming host cells *in vivo* are encompassed within the field of gene therapy, which was unpredictable at the time the claimed invention was filed and has remained unpredictable thereafter. The skilled artisan could not rely on the state of the gene therapy art for practicing the invention as claimed due to the unpredictable nature of expressing a heterologous nucleotide in a host

cell *in vivo*. It is maintained that the instant specification has failed to provide teachings, guidance, or working examples that would allow the skilled artisan to transform and express a foreign DNA sequence in a host cell *in vivo*. It is further maintained that the evidence of record has failed to teach how to target cells in vivo, the mode of administration of an expression construct, the level of expression of a heterologous nucleotide sequence necessary to provide therapeutic benefit, and the fate of the expressed heterologous protein *in vivo*. See pages 6-7 of the Office action mailed on 1/3/02. The unpredictability of the gene therapy art is discussed in Verma el and Anderson et al, which support the Examiner's arguments (above). See pages 7-8 of the Office action mailed on 1/3/02. In contrast to Applicant's opinion that methods of gene therapy were well known (and presumably enabled) at the time the claimed invention was filed Verma and Anderson both teach that human diseases have not been successfully treated by gene therapy. Verma and Anderson compare and contrast various vectors available for gene therapy applications and their respective limitations. The evidence of record has not provided adequate guidance to overcome the unpredictability of the gene therapy art as discussed by Verma and Anderson.

In addition, in the previous Office action the Examiner stated the claimed invention was only enabled to the extent of the nucleotide sequence set forth in SEQ ID NO: 1. See the sentence bridging pages 6-7 of the Office action mailed on 1/3/02. However, the Examiner did not fully explain why the variant nucleotide sequences were not enabled. As such an explanation to that end is

included below. The specification has not taught any nucleotide sequences having at least 87% or 95% identity to SEQ ID NO: 1 or any nucleotide sequences that hybridize to the nucleotide sequence set forth in SEQ ID NO: 1 (termed variants hereafter) that function as an ABC promoter. The skilled artisan would not be able to predict the structure of a variant that is biologically active because the specification has not provided any information as to the structural elements required for a variant to be biologically active. The specification does not provide any information on what nucleotides are necessary and sufficient for biological activity. The specification also provides no teachings on what nucleotide sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in a variant nucleotide sequence that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity of the sequence. Since there are no examples of a variant known to have structural homology with SEQ ID NO: 1, it is not possible to even guess at the nucleotides which are critical to its structure or function based on sequence conservation. Furthermore, it is known in the art that nucleotide substitutions can adversely affect biological activity if nucleotides that are critical for such functions are substituted. Even a single base substitution can affect the ability of a nucleotide sequence to function as a promoter. Huang et al (PNAS, 1998, 95: 14669-14674) support this observation. Huang et al report that a single base mutation in the ζ-globin promoter repressed transcription of the human ζ-globin gene in a transgenic mouse study. See abstract and pages 14669, and 14672. Consequently, excessive trial and error

experimentation would have been required to identify the necessary nucleic acid sequence derivatives to obtain biologically active variant transcriptional regulatory sequence with a nucleotide sequence differing from SEQ ID NO: 1 since the nucleotide sequence of such variants could not be predicted.

It would have required undue experimentation to predict the structures of variants to the claimed sequences that would be biologically active in the absence of a functional assay, without a reasonable expectation of success.

Accordingly, the rejection is maintained for the reasons of record.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 49 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49 is indefinite as written. The claim has been amended to recite an isolated human ABC 1 gene comprising at least 6 exons and a promoter. The specification however has described the ABC 1 gene to span a minimum of 70KB and to contain at least 49 exons. The ABC 1 gene as defined by the claim as amended is not consistent with the definition provided by the specification. Correction is required.

Allowable Subject Matter

Claim 2 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS
PATENT EXAMINER